

CLAIMS

1. Use of a nucleotide sequence selected among:

- (i) a nucleotide sequence comprising the DNA sequence identified under No. 1, and represented on Figure 14A, or under No. 3 and represented on Figure 14B ;
- (ii) a nucleotide sequence encoding a polypeptide having the amino-acid sequence identified under No. 2, and represented on Figure 15A or encoding a polypeptide having the amino-acid sequence identified under No. 4 and represented on Figure 15B;
- (iii) a nucleotide sequence comprising the DNA sequence identified under No. 5, and represented on Figure 14C ;
- (iv) a nucleotide sequence encoding a polypeptide having the amino-acid sequence identified under No. 6, and represented on Figure 15C;
- (v) a nucleotide sequence derived from sequence defined under (i), (ii), (iii) or (iv) wherein said sequence is modified particularly by deletion, addition or substitution of one or more nucleotides providing that the resulting nucleotide sequence encodes a polypeptide capable of binding a nucleotide sequence designated IPCS which comprises the DNA sequence AAATGNNNNC, wherein N means any nucleotide (G, A, C or T(U))

for the expression in a determined eucaryotic cell, of a polypeptide capable of interacting with said nucleotide sequence designated IPCS and capable of acting as a positive transcription factor for the transcription of a nucleotide sequence placed under the control of said IPCS sequence and present in said eucaryotic cell.

2. Use of a nucleotide sequence according to claim 1 for the expression of a polypeptide acting as a positive transcription factor for a gene chosen among

genes involved in the control of cellular growth, cellular proliferation, cellular differentiation or cellular apoptosis.

3. Use according to claim 1 or 2 wherein the nucleotide sequence comprises the cDNA corresponding to a 2.5kb coding sequence of the transcript of the PRDII-BF1 gene.

4. Use according to claim 3 wherein a start codon is added upstream from exon III of the PRDII-BF1 gene.

5. Use according to claim 3 wherein the nucleotide sequence comprises the succession of exons III, V, VI, VII, VIII and IX of the PRDII-BF1 gene, said nucleotide sequence being devoid of exon IV of said PRDII-BF1 gene in the case of GAAP-1 and containing the first 45 nucleotides of exon IV in the case of GAAP-2.

6. Use according to anyone of claims 1 to 3 in which the nucleotide sequence codes for a GAAP-1 polypeptide comprising the amino acid sequence identified under No. 2 or under No. 4 or for a GAAP-2 polypeptide comprising the amino acid sequence identified under No. 6.

7. Use according to anyone of claims 1 to 5, wherein the nucleotide sequence codes for a variant of the GAAP-1 polypeptide or the GAAP-2 polypeptide, said variant being derived from GAAP-1 or GAAP-2 by insertion, deletion or substitution of one or several amino acid residues, provided it retains the property of GAAP-1 or GAAP-2 to bind an IPCS sequence and to act as a transcriptional factor for the transcription of a nucleotide sequence placed under the control of said IPCS sequence and present in a eucaryotic cell.

8. Use according to anyone of claims 1 to 6 in which the nucleotide sequence hybridises under stringent conditions with the DNA sequence identified under No. 1 or identified under No. 3 or with the DNA sequence identified under No. 5.

9. Use of a nucleotide sequence according to anyone of claims 1 to 8, wherein said nucleotide sequence is placed under the control of a promoter sequence selected among constitutive or inducible promoters.

10. Use of a nucleotide sequence according to anyone of claims 1 to 9 wherein the eucaryotic cells are malignant cells.

11. Use according to anyone of claims 1 to 10 wherein the eucaryotic cells are those of a developed tumor.

12. Use of a nucleotide sequence according to anyone of claims 1 to 9 for the control of cell apoptosis.

13. Use of a nucleotide sequence according to anyone of claims 1 to 12 wherein the positive regulation of transcriptional activity is obtained for a gene selected among p53, IRF1, Rb, p21 (WAF1), p27, wt1, bax, TNF receptor and FAS.

14. Use of a nucleotide sequence according to anyone of claims 1 to 13 wherein the positive regulation of transcriptional activity allows regulation of transcription of several genes in the treated cells.

15. Nucleotide sequence comprising the DNA sequence identified under No. 1, said nucleotide-sequence being devoid of the sequence forming exon IV in the PRDII-BF1 gene.

16. Nucleotide sequence according to claim 15 which consists of the DNA sequence identified under No. 1.

17. Nucleotide sequence derived from the nucleotide sequence according to anyone of claims 15 or 16 and which is selected from the group consisting of:

- (i) a fragment of the DNA sequence identified under No. 1 (Figure 14A), or a fragment of the DNA sequence identified under No. 3 (Figure 14B) which can be used as a specific probe to detect the presence of said DNA sequence identified under No. 1, No. 3, or No. 5 or a mutated sequence thereof,
- (ii) a nucleotide sequence encoding a polypeptide having the amino-acid sequence identified under No. 2, or a nucleotide sequence encoding a polypeptide having the amino-acid sequence identified under No. 4 or a nucleotide sequence encoding a polypeptide having the amino-acid sequence identified under No. 6,
- (iii) a nucleotide sequence derived from sequence defined under (i) or (ii) wherein said sequence is modified, especially by deletion, addition or substitution of one or more nucleotides providing that the resulting nucleotide sequence encodes a polypeptide capable of binding a nucleotide sequence designated IPCS which comprises the DNA sequence AAATGRYKKC, and is capable when used in appropriate conditions, of expressing in a determined eucaryotic cell, a polypeptide interacting with the nucleotide sequence designated IPCS and acting as a positive transcriptional factor for the

transcription of a nucleotide sequence placed under the control of said IPCS sequence and present in said eucaryotic cell.

18. Nucleotide sequence which is contained on plasmid pGAAP1 deposited at the ECACC under n° 01052921 on May 29, 2001.

19. Recombinant polypeptide, being the product of the expression in a eucaryotic cell, of a nucleotide sequence coding for a polypeptide capable of interacting with the nucleotide sequence designated IPCS and capable of acting as a positive transcription factor for the transcription of a nucleotide sequence placed under the control of said IPCS sequence and present in said eucaryotic cell.

20. Recombinant polypeptide, being the product of the expression in a eucaryotic cell, of a nucleotide sequence according to anyone of claims 15 to 18.

21. Recombinant polypeptide according to anyone of claims 19 to 20 which regulates the transcriptional activity of a gene selected among p53 and IRF1 when it is expressed in a eucaryotic cell constitutively expressing said gene.

22. Recombinant polypeptide according to anyone of claims 19 to 21 which has an apparent molecular weight of 75 kDa by SDS PAGE electrophoresis.

23. Recombinant polypeptide, being the expression product in a eucaryotic cell selected among mammal cells, of a nucleotide sequence according to anyone of claims 15 to 18, said recombinant polypeptide including post translational modification enabled in said eucaryotic cell.

24. Recombinant polypeptide according to anyone of claims 19 to 23 which comprises the amino acid sequence identified under No. 2 or the amino acid sequence identified under No. 4, or the amino acid sequence identified under No. 6.

25. Recombinant polypeptide according to anyone of claims 19 to 23 which comprises a fragment of the amino acid sequence identified under No. 2 provided the polypeptide is capable of interacting with the nucleotide sequence designated IPCS to act as a positive transcription factor for the transcription of a nucleotide sequence placed under the control of said IPCS sequence and present in said eucaryotic cell.

26. Recombinant eucaryotic cell which is recombined by insertion of a nucleotide sequence according to anyone of claims 15 to 18.

27. Recombinant eucaryotic cell according to claim 26 which expresses the polypeptide encoded by the inserted nucleotide sequence.

28. Recombinant eucaryotic cell according to claim 26 or 27 which is a cell selected among cells normally expressing genes involved in the control of cell growth, cell differentiation, cell proliferation or cell apoptosis.

29. Recombinant eucaryotic cell according to anyone of claims 26 to 28 which is a malignant cell.

30. Recombinant eucaryotic cell which is recombined with a nucleotide sequence encoding a polypeptide capable of binding a nucleotide sequence designated IPCS and comprising the DNA sequence AAATGNNNNC, to enable, in appropriate conditions, the expression of a polypeptid capable of

interacting with the nucleotide sequence designated IPCS and capable of acting as a positive transcriptional factor for the transcription of a nucleotide sequence placed under the control of said IPCS sequence and present in said eucaryotic cell.

31. Recombinant eucaryotic cell according to anyone of claims 26 to 30 wherein the polypeptide comprises the aminoacid sequence identified under No. 2, or the amino acid sequence identified under No. 4, or the amino acid sequence identified under No. 6.

32. Recombinant eucaryotic cell according to anyone of claims 26 to 31 which is selected among U937, K562, SK-N-SH, MCF7, KG1, TF1.

33. Recombinant vector which is recombined with an insert consisting of a nucleotide sequence according to anyone of claims 15 to 18.

34. Recombinant vector according to claim 33 which is an expression vector suitable for expression of said insert, in a eucaryotic cell.

35. Recombinant vector according to claim 34 which is suitable for transient or controlled expression of said insert.

36. Recombinant vector according to anyone of claims 34 or 35 wherein said insert is placed under the control of a promoter regulated by a physiologically acceptable compound.

37. Recombinant vector according to anyone of claims 34 or 35 wherein the transcription of said insert is placed under the control of an exogenous transactivating system.

38. Recombinant vector according to anyone of claims 34 to 37 which is suitable for gene therapy.

39. Recombinant vector according to claim 38 which is selected among viral, retroviral, lentiviral, poxviral, adenoviral, AAV vectors.

40. Composition suitable for a therapeutic use which comprises a nucleotide sequence according to anyone of claims 15 to 18 or a recombinant cell according to anyone of claims 26 to 32, or a recombinant polypeptide according to anyone of claims 19 to 25.

41. Composition according to claim 40 which is used in combination with a therapeutic agent selected among antiviral agents and anticancer agents wherein said combined use is permitted by the time - or site - associated or separated use of the composition and of the therapeutic agent.

42. Composition according to claim 41 wherein the anticancer agent is an immuotherapeutic agent, a chemotherapeutic agent or is radiotherapy.

43. Composition according to anyone of claims 40 to 42 for the treatment of a malignant cell.

44. Use of a nucleotide sequence according to anyone of claims 15 to 18 or of a recombinant cell according to anyone of claims 26 to 32, or a recombinant polypeptide according to anyone of claims 19 to 25, for the preparation of a biological tool for screening compounds capable of interacting with an IPCS sequence present in the promoter sequence of a gene involved in the control of cellular growth, cellular proliferation, cellular differentiation or cellular

apoptosis, and capable of regulating the transcription of a nucleotide sequence placed under the control of said IPCS sequence.

45. Process for the in vitro detection of a deficient BRDII-BFI gene comprising the steps of:

- contacting a probe constituted from the nucleotide sequence identified under No. 1 or under No. 3 or under No. 5 or a fragment thereof comprising the zinc finger binding domains corresponding to the domains localised within exon VI of the BRDII-gene, with the DNA of a cell normally constitutively expressing said gene, in stringent conditions,
- detecting the hybridisation product between said probe and said cell DNA.

46. Process for the in vitro detection of a deficient transcriptional activity of genes involved in the control of cell growth, cell differentiation, cell proliferation or cell apoptosis, comprising the step of detecting a deficient production of the transcript of said gene which would normally encode a polypeptide capable of binding an IPCS sequence and as a result would positively regulate the transcription of a nucleotide sequence placed under the control of said IPCS sequence.

47. Process for the in vitro detection of a prognostic for transformation of cells toward a malignant state, which comprises the step of detecting a mutation in the PRDII-BFI gene normally expressed in said cells, or detecting a mutation in the transcript obtained by splicing of said gene, which mutation would result in lack of expression or in an abnormal expression of polypeptide expression product of said PRDII-BF1 gene capable of binding to an IPCS sequence.

48. Process for the screening of compounds capable of regulating the transcriptional activity of genes containing an IPCS sequence in their promoter

region, said genes being active in the control of cell growth, cell differentiation, cell proliferation, or cell apoptosis, said process comprising the steps of :

- contacting the assayed compounds with the DNA of a cell expressing genes containing an IPCS sequence in their promoter region,
- detecting a DNA-compound complex formation and assaying its transcriptional activity on said gene containing the IPCS sequence.

49. Use of a recombinant polypeptide according to anyone of claims 19 to 25 for screening molecules suitable for use as agonist of GAAP-1 or of GAAP-2.

50. Use of a recombinant polypeptide according to anyone of claims 19 to 25 for screening molecules suitable for use as antagonist of GAAP-1 or of GAAP-2.